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Human Disease Consequences of Fiber Exposures: A Review of Human Lung Pathology and Fiber Burden Data

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Inhalation of asbestos fibers results in a variety of neoplastic and nonneoplastic diseases of the respiratory tract. Some of these diseases, such as asbestosis, generally occur after prolonged and intensive exposure to asbestos, whereas others, such as pleural mesothelioma, may occur following brief exposures. Inhalation of nonasbestiform mineral fibers can occur as well, and these fibers can be recovered from human lung tissue. Thus, there has been considerable interest in the relationship between mineral fiber content of the lung and various pathologic changes. Techniques for fiber analysis of human tissues have not been standardized, and consequently results may differ appreciably from one laboratory to another. In all reported series, extremely high fiber burdens are found in the lungs of individuals with asbestosis. Although there is a correlation between the tissue concentration of asbestos fibers and the severity of pulmonary fibrosis, further studies of the mineralogic correlates of fiber-induced pulmonary fibrosis are needed. Mesothelioma may occur with fiber burdens considerably less than those necessary to produce asbestosis. More information is needed regarding the migration of fibers to the pleura and the numbers, types, and dimensions of fibers that accumulate at that site. Patients with asbestosis have a markedly increased risk for lung cancer, but the risk of lung cancer attributable to asbestos in exposed workers without asbestosis who also smoke is controversial. Combined epidemiologic-mineralogic studies of a well-defined cohort are needed to resolve this issue. In addition, more information is needed regarding the potential role of nonasbestos mineral fibers in the pathogenesis of lung cancer.

Introduction

The development of techniques for assaying the mineral fiber content of tissues has provided researchers with the opportunity to correlate the occurrence of various fiber-related diseases with the cumulative fiber burdens in the target organ. Exposure to asbestos generally occurs through the inhalation of airborne fibers, and thus the respiratory tract is the site of most asbestos-related diseases. Consequently, most studies of tissue fiber burdens have concentrated on the analysis of lung parenchyma. Asbestos is both fibrogenic and carcinogenic with respect to the respiratory system, with diseases occurring in the pleura (pleural plaques, diffuse pleural fibrosis, malignant mesothelioma) and in the lung (asbestosis, bronchogenic carcinoma). The pathologic features of these diseases have been reviewed in detail elsewhere (*1–4*) and will be discussed only insofar as they relate to lung fiber burdens.

Asbestos is not a single mineralogic entity, but rather a group of mineralogic species that share the properties of high tensile strength, flexibility, and relative thermal and chemical resistance. Two major groups of asbestiform minerals include serpentines and amphiboles. Chrysotile asbestos is the sole representative of the serpentine group, and its structure, chemical composition, and persistence in biological systems differs appreciably from those of the amphiboles. Commercially valuable forms of amphibole asbestos include amosite and crocidolite. Other amphiboles, including actinolite, anthophyllite, and tremolite, have little or no commercial value but may be found as contaminants of a variety of other mineral substances. Details of the physical and chemical properties of the various asbestiform minerals have been reviewed elsewhere (*5*). In addition, a variety of nonasbestiform fibrous minerals may be identified in human lung tissue samples, including talc and other silicates, silica, carbon, metal oxides (such as titanium, iron, or aluminum), zeolites, and man-made mineral fibers (*6–8*).

It is the purpose of this review to discuss various aspects of human lung fiber burden data as they relate to pulmonary disease. This will include a critical review of techniques for analyzing lung fiber burdens and the limitations of extrapolating results from one laboratory to another. The results of mineral fiber analysis in specific diseases, including asbestosis, mesothelioma, benign pleural diseases, and carcinoma of the lung, will also be evaluated. Finally, areas where there are gaps in our knowledge will be specifically identified, with suggestions for future research directions.

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Techniques for Analysis of Pulmonary Fiber Burdens

Several techniques have been devised for assaying mineral fiber content of human lung tissue (*7,9–12*). These techniques generally involve three basic steps: *a*) dissolution and removal of the organic matrix material of the lung in which the fibers are embedded; *b*) recovery and concentration of the mineral fibers; and *c*) analysis of the mineral fiber content by some form of microscopy. As summarized in Table 1, the actual analytical result obtained on any one sample can be profoundly influenced by the steps in the analytical procedure employed by the investigator. Indeed, interlaboratory comparison trials have shown that striking differences can occur between laboratories even when the same sample is analyzed (*13*). An ongoing international interlaboratory comparison study is now drawing to its close, and should provide information regarding which steps in the analysis produce the greatest discrepancies. In addition, intralaboratory variation can occur, which may be either due to changes in a laboratory's procedures over time (*14*) or to variation in fiber content from one site to another within the lung (*15,16*).

Such interlaboratory variation makes it difficult to compare results obtained by different laboratories. This does not necessarily invalidate the results of human fiber burden studies, since there is evidence for internal consistency within individual laboratories (*13*). Rather, one must cautiously compare results between laboratories, keeping in mind differences in analytical techniques. Furthermore, when interpreting fiber burden data, one must realize that the analysis is occurring at a single point in time, usually when advanced disease is present. The fiber burden at that point may or may not relate to the tissue fiber content at the time when disease was actively evolving—a period of great interest to investigative biologists. Nonetheless, there is a growing consensus that the fiber burdens which accumulate in the lung are the primary determinant of subsequent disease (*17*).

Table 1. Factors affecting fiber burden data.

Digestion procedure
Wet chemical digestion (alkali, enzymes)
Low temperature plasma ashing
Number of sites sampled
Recovery procedure
Use of a centrifugation step
Use of a sonication step
Filtration step (type of filter, pore size)
Analytical procedure
Microscopic technique (LM, PCM, TEM, SEM)[a]
Magnification used
Sizes of fibers counted and other counting rules
Numbers of fibers or fields actually counted
Reporting of results
Asbestos bodies or fibers (or both combined)
Sizes of fibers counted
Concentration of fibers (per gram wet or dry lung or per cubic centimeter)

[a] LM, light microscopy; PCM, phase contrast microscopy; TEM, transmission electron microscopy; SEM, scanning electron microscopy.

Asbestosis

Asbestosis is by definition pulmonary interstitial fibrosis developing in response to inhalation of asbestos fibers. The minimal histologic criteria for the diagnosis of asbestosis include peribronchiolar fibrosis associated with accumulations of asbestos bodies (*2,18*). Some investigators have challenged the requirement for finding asbestos bodies in histologic sections, since some workers are exposed almost exclusively to chrysotile-containing products (*19*), and chrysotile forms asbestos bodies less readily than amphibole asbestos fibers (*20*). However, studies of chrysotile miners and millers (*21*) and my own observations of textile workers exposed to chrysotile fiber show that asbestos bodies are readily found in histologic sections of individuals with asbestosis. Furthermore, these asbestos bodies can be shown by means of energy dispersive spectrometry to have chrysotile cores (*21,22*).

Several studies have examined the asbestos content of lung tissue in series of patients with asbestosis (*18,23–26*). These data are summarized in Table 2. The values obtained are roughly similar among the reported series, with the exception of the unusually high median count for asbestos bodies in the study by Ashcroft and Heppleston (*24*) and the high mean count for uncoated fibers by electron microscopy in the study by Wagner et al. (*26*). Most of the discrepancies can be explained by methodologic differences. For example, Whitwell et al. (*23*) used phase contrast light microscopy (PCLM) and counted all fibers greater than or equal to 6 μm in length, counting coated and uncoated fibers together. Ashcroft and Heppleston (*24*) used PCLM at a magnification of 400× and counted all visible fibers, enumerating coated and uncoated fibers separately. Warnock et al. (*25*) used transmission electron microscopy (TEM) and counted all fibers exceeding 0.25 μm in length. Wagner et al. (*26*) used the PCLM method of Ashcroft and Heppleston (*24*) as well as TEM. Roggli (*18*) used scanning electron microscopy (SEM) at a magnification of 1000× to count all fibers with length greater than or equal to 5 μm. Both Warnock et al. (*25*) and Roggli (*18*) counted asbestos bodies by conventional light microscopy. The median uncoated fiber count exceeds one million (10^6) fibers per gram of dried lung in all five studies. When these values are compared to the background levels of pulmonary fiber burden in the general population as reported by various laboratories (*18,23,26,27*), it is observed that patients with asbestosis generally have extremely high fiber burdens.

These observations fit well with epidemiologic data, which indicate that asbestosis generally occurs in individuals with prolonged and heavy exposure to airborne asbestos fibers (*28*). In addition, the data suggest that analysis of tissue asbestos burdens may be useful

Table 2. Asbestos content of lung tissue in reported series of patients with asbestosis (*18*).[a]

No. of cases	Method[b]	Asbestos bodies/g dried lung	Uncoated fibers/g dried lung	Reference
23	PCLM	—	8 (1.0–70)	(*23*)
22	PCLM	12.2 (0.49–192)	32 (1.3–493)	(*24*)
100	PCLM	—	1.5 (0.001–31.6)	(*26*)
76	SEM[c]	0.378[d] (0.006–16)	3.3[d] (0.18–125)	(*18*)
22	TEM[c]	0.123 (0.001–7.38)	5.68 (1.6–121)	(*25*)
170	TEM	—	372 (< 1.0–10,000)	(*26*)

[a] Values reported are the median counts for millions (10^6) of asbestos bodies or uncoated fibers per gram of dried lung tissue, with ranges indicated in parentheses, except for the study of Wagner et al. (*26*), where only the mean value could be obtained from the data presented.
[b] PCLM, phase contrast light microscopy; SEM, scanning electron microscopy; TEM, transmission electron microscopy.
[c] In these two studies, asbestos bodies were counted by conventional light microscopy.
[d] Values multiplied by a factor of 10 (approximate ratio of wet to dry lung weight) for purposes of comparison.

for distinguishing asbestosis from other types of interstitial fibrosis, including idiopathic varieties. Although this distinction can be made in the vast majority of cases by the identification of asbestos bodies in histologic section (*2,18*), cases have been reported in which asbestos bodies could not be demonstrated histologically (*29,30*). The problem is to determine what level of fiber burden should be required to diagnose asbestosis in cases where asbestos bodies are not found in tissue sections. Most of the data for uncoated fibers (Table 2) relate to fibers which are 5 μm or greater in length and suggest that at least a million fibers per gram of dry lung tissue should be present. This level is further supported by the study of Roggli (*18*) correlating the histologic severity of asbestosis with the tissue burden of uncoated fibers 5 μm or greater in length. The regression line in this study had an intercept of 100,000 fibers/g wet lung (approximately 10^6 fibers/g dry lung) at a histologic score of 0 (i.e., no fibrosis).

Whereas the pathogenicity of asbestos fibers 5 μm or greater in length is well established, that of shorter fibers remains unproven (*31,32*) and is an area requiring further investigation. The problem is compounded by the fact that short chrysotile fibers are a ubiquitous contaminant, they are difficult to count accurately (*33*), and they may be found in substantial numbers within lung tissues of individuals from the general population (*27*). There is insufficient data in the literature to suggest any level of short fibers as a criterion for the diagnosis of asbestosis. Short fibers are usually present in lung tissue in substantially greater numbers than long fibers (i.e., $\geq$ 5 μm in length) (*11,27*). Therefore, it is difficult to accurately assess the numbers of long fibers that are present in studies employing TEM to count all visible fibers at a high magnification (e.g., 20,000× or greater). One suggestion for future correlative pathology fiber burden studies employing TEM is the use of a stratified counting scheme that takes into account the numbers and dimensions of both short and long fibers.

Although there is a good correlation between numbers of fibers per gram of lung tissue and severity of pulmonary interstitial fibrosis (*18,23–26*), there is a wide scatter in the data, indicating that factors other than tissue fiber burden are involved in determining the ultimate degree of fibrosis which develops (*18,24*). In this regard, studies by Timbrell et al. (*34,35*) have shown that in individuals exposed to the various types of amphibole asbestos, the severity of pulmonary fibrosis correlates better with the relative fiber surface area per unit weight of tissue than with the relative fiber number or mass, as determined by magnetic alignment and light scattering. These observations need to be confirmed by electron microscopic techniques that take into account not only fiber number, mass, and relative surface area, abut also fiber dimensions and in particular absolute numbers of long fibers. In addition, it is necessary to determine which if any of these factors apply to asbestosis due to the inhalation of chrysotile. A recent study in this regard by Churg et al. (*36*) showed a direct correlation between fiber concentration and severity of fibrosis for both chrysotile and contaminating tremolite fibers, but no correlation of fibrosis with fiber size, surface area, or mass for chrysotile and an inverse correlation with fiber length, aspect ratio, and surface area for tremolite. Clearly, further studies of the mineralogic correlates of fiber-induced pulmonary fibrosis are needed.

Mesothelioma

Mesothelioma is a malignant tumor that derives from the serosal lining of the body cavities. The most common

site of origin is the pleura, followed by the peritoneum and pericardium. The pathologic features of these tumors have been reviewed elsewhere (*2,37,38*). Mesothelioma is a rare form of malignancy, and its occurrence is strongly associated with exposure to asbestos fibers decades prior to the development of clinical symptoms (*1,28,39*). Epidemiologic studies have shown that mesothelioma can develop years after brief or low level exposures, and recent studies have indicated that there are cases of mesothelioma for which no prior exposure to asbestos can be identified (*37,40,41*). Therefore, there has been considerable interest in the mineral fiber content of the lung in patients with mesothelioma.

Several studies have examined the asbestos content of lung tissue in series of patients with mesothelioma (*23,42–47*). These data are summarized in Table 3. Comparison with the data in Table 2 shows that there is considerable overlap of fiber content among patients with asbestosis and mesothelioma. This is not surprising, since according to Antman (*48*), about 20% of patients with pleural mesothelioma also meet criteria for asbestosis [26% in the series of Whitwell et al. (*23*), 21% in the series of Roggli et al. (*46*)]. Studies examining the pulmonary fiber burdens in groups of patients with asbestosis versus mesothelioma have shown that mesothelioma may occur with fiber burdens considerably less than are required to produce asbestosis (*23,46*). This observation is in agreement with the epidemiologic findings noted above. One very important exception to this observation has been reported in miners and millers of chrysotile asbestos (*49*). In these patients, the total fiber burden in chrysotile workers with mesothelioma is considerably greater than the median fiber concentrations in workers with asbestosis. Furthermore, the ratio of tremolite (a contaminant of chrysotile ore) to chrysotile is considerably greater in the lungs of the workers with mesothelioma than in the workers with asbestosis (*44,49*). These observations and scattered reports of mesothelioma occurring in individuals exposed environmentally to tremolite have led some investigators to propose that it is the tremolite component of the chrysotile ore which is responsible for the development of mesothelioma in chrysotile mine workers (*49*).

In consideration of Stanton's observations that fibers greater than 8.0 μm in length and less than 0.25 μm in diameter are the most efficient at producing mesothelioma experimentally (*50*), it is of interest to examine fiber dimension data in studies of human lungs with regard to mesothelioma. The study by Churg and Wiggs (*43*) of amphibole-induced mesothelioma showed that 39% of amosite fibers and 23% of crocidolite fibers were 5 μm or greater in length. In contrast, the study by Churg et al. (*44*) of chrysotile-related mesotheliomas showed that only 11% of chrysotile fibers and 13% of tremolite fibers exceeded 5 μm in length. The vast majority of fibers in both studies were less than 0.25 μm in diameter (*43,44*). Lippmann (*35*) concluded in his review of the human and animal data that it is primarily fibers greater than 5 μm in length and less than 0.1 μm in diameter that are responsible for the development of mesotheliomas. The fiber dimension and fiber burden data from chrysotile versus amphibole-induced mesothelioma in humans are consistent with either the hypothesis that *a*) large numbers of short (<5 μm) asbestos fibers are carcinogenic for the pleura in man, or that *b*) large burdens are necessary to provide sufficient

Table 3. Asbestos content of lung tissue in reported series of patients with mesothelioma.[a]

No. of cases	Method[b]	Asbestos bodies/g dried lung	Uncoated fibers/g dried lung	Reference
100	PCLM	—	0.75 (0–70)	(*23*)
15	SEM	—	11 (2–490)	(*42*)
14	SEM	—	2.4 (0.4–37)	(*45*)
19	SEM[c]	48[d] (0.002–9770)	0.81[d] (0.012–28.9)	(*46*)
10	TEM	—	3.5 (0.1–85.2)	(*43*)
6	TEM	—	238 (52–2190)	(*44*)
20	TEM[c]	3.2 (0.04–450)	18	(*47*)

[a] Values reported are the median counts for thousands (10^3) of asbestos bodies or millions (10^6) of uncoated fibers per gram of dried lung tissue, with ranges indicated in parentheses, except for the study of Gaudichet et. al. (*47*), where only the mean value for total fibers per gm dried lung could be obtained from the data presented.

[b] PCLM, phase contrast light microscopy; SEM, scanning electron microscopy; TEM, transmission electron microscopy.

[c] In these two studies, asbestos bodies were counted by conventional light microscopy.

[d] Values multiplied by a factor of 10 (approximate ratio of wet to dry lung weight) for purposes of comparison.

numbers of "Stanton-sized" tremolite fibers. However, the data are also consistent with a third possibility: due to chrysotile's fragility and tendency to break into small individual fibrils, very high exposure levels are necessary to maintain a sufficient level of "Stanton-sized" chrysotile fibers in contact with the pleura. This latter hypothesis may be applicable to possible mesothelioma risks from nonasbestos mineral fibers, such as manmade mineral fibers, many of which are either soluble *in vivo* (*51*) or tend to fracture transversely, resulting in shorter fibers that may be more readily cleared from the lung (*52*).

An area requiring further study is the migration and distribution of amphibole versus chrysotile fibers to the visceral and parietal pleura. It is reasonable to assume that fibers actually reaching the pleura are the ones responsible for diseases of the pleura, and the dimensions and types of fibers accumulating in the pleura are not necessarily similar to those accumulating in the lung parenchyma. In this regard, Sebastien et al. (*53*) reported that in individuals exposed to mixtures of fibers, there was a relative accumulation of longer amphibole fibers in the lung parenchyma, whereas short chrysotile fibers accumulate in the pleura. However, Churg et al. (*44*) were unable to find a difference in the size or type of fibers isolated from peripheral versus central lung parenchyma in Canadian chrysotile workers. One problem with such studies is that samples of peripheral lung necessarily include a large proportion of lung parenchyma, so that any differences between fiber content of lung parenchyma and visceral pleura *per se* would be masked or minimized. Although there are substantial data now available on the fiber content of lung parenchyma from the general population with various analytical techniques (*23,27,46,47*), no comparable data exist for the visceral and parietal pleura. Furthermore, the migration of fibers from the lungs to the peritoneal cavity needs to be further clarified.

Benign Pleural Disease

The most common pathologic abnormality related to the inhalation of asbestos fibers is the parietal pleural plaque. These lesions occur as circumscribed, elevated areas of pleural thickening with a cartilaginous consistency, located most often over the domes of the diaphragm or along the posterolateral chest wall overlying the ribs (*2*). They are ivory colored with a smooth or knobby surface (the latter resembling candle wax drippings), and may be calcified. Other pleural abnormalities related to asbestos exposure include diffuse visceral pleural fibrosis, rounded atelectasis, and benign asbestos pleural effusion. These abnormalities apparently result from inflammation and repair stimulated by asbestos fibers reaching the pleural surface. Epidemiologic studies indicate that benign asbestos-related pleural diseases may develop following brief or low level exposures (*1,28*).

Several studies have examined the asbestos content of lung tissue in series of patients with benign asbestos-related pleural disease (*42,54–57*). Most of these have dealt with parietal pleural plaques, and the studies are summarized in Table 4. These data show that patients with parietal pleural plaques have tissue fiber burdens that are on the average substantially lower than those of patients with asbestosis (Table 2 vs Table 4) and are somewhat lower than but of about the same order of magnitude as patients with mesothelioma (Table 3 vs Table 4). The studies by Warnock et al. (*54*) and Churg (*55*) both showed a significant increase in the concentrations of commercial amphiboles (amosite or crocidolite) in the lungs of patients with plaques as compared to a reference population, but no significant differences for chrysotile or noncommercial amphiboles. Whitwell et al. (*23*) included 21 patients with pleural plaques in their normal control series of 100 cases, and found that 55% of the cases with more than 20,000 fibers/g by PCLM but only 5.5% of cases with fewer than 20,000 fibers/g had plaques. All of these observations support a role for asbestos fibers in the production of pleural plaques and confirm the epidemiologic findings that plaques may develop following brief or low-level exposures. The study of patients with diffuse pleural fibrosis by Stephens et al. (*57*) indicates that these patients have on the average a greater fiber burden than patients with plaques alone, but less than patients with asbestosis (Table 2 vs Table 4).

Many of the questions raised in the previous section with respect to mesothelioma also apply to benign asbestos-related pleural disease, particularly in regard to migration of fibers to the pleura. The mechanism of formation of pleural plaques and their peculiar localization to the parietal pleura is poorly understood, especially in terms of the dimensions and types of fibers that gain access to this compartment.

Carcinoma of the Lung

The association between asbestos exposure and an increased risk for lung cancer has been well-established epidemiologically (*1,28,32*), and cigarette smoking and asbestos appear to act in a synergistic fashion to increase this risk (*58*). The pathologic features of lung cancer among asbestos workers are similar to those of nonexposed cigarette smokers, showing the same distribution of histologic patterns (*46,59*). There is an increased predominance of lower lobe cancers among asbestos workers in contrast to the upper lobe predominance in nonexposed cigarette smokers (*60*). The association between asbestos-exposure and lung cancer is widely accepted for patients with asbestosis, and some investigators have proposed the concept that these tumors are scar cancers. However, only a minority of cases fit the classic concept of a peripheral scar carcinoma, and most are the usual bronchogenic carcinoma. Whether lung cancers occurring in cigarette smoking asbestos workers without asbestosis can be partly attributed to the asbestos exposure is a highly controversial issue (*61–66*). It is therefore of interest

Table 4. Asbestos content of lung tissue in reported series of patients with benign asbestos-related pleural disease.[a]

No. of cases	Method[b]	Asbestos bodies/g dried lung	Uncoated fibers/g dried lung	Reference
14	SEM	—	2.2 (0.1–13)	(*42*)
17	SEM	48.7[c] (0–408)	0.5[c] (0.007–1.74)	(*56*)
20	TEM[d]	7.8[c] (0.3–9,600)	0.54[c] (0.018–71)	(*54*)
29	TEM[d]	17.3[c] (0–194)	1.14[c] (ND)	(*55*)
7[e]	PCLM	—	0.131 (0.029–0.378)	(*57*)
	TEM	—	28.9 (9.2–83.5)	

[a] Values reported are the median counts for thousands (10^3) of asbestos bodies or millions (10^6) of uncoated fibers per gram of dried lung tissue, with ranges indicated in parentheses, except for the study of Churg (*55*), where only the mean value for total fibers per gram was given and a range could not be determined (ND).
[b] PCLM, phase contrast light microscopy; SEM, scanning electron microscopy; TEM, transmission electron microscopy.
[c] Values multiplied by a factor of 10 (approximate ratio of wet to dry lung weight) for purposes of comparison.
[d] In these two studies, asbestos bodies were counted by conventional light microscopy.
[e] Cases in series of Stephens et al. (*57*) are diffuse pleural fibrosis. All others are parietal pleural plaques.

to review what has been learned from fiber burden analysis in this regard.

Several studies have examined the asbestos content of lung tissue in series of patients with lung cancer (*23,25,47,56,67*) and these data are summarized in Table 5. The values reported depend not only on the analytical techniques employed by the various authors, but on the way the cases were selected as well. Whitwell et al. (*23*) examined 100 consecutive cases of lung cancer and found very similar results between cancer cases and controls. Gaudichet et al. (*47*) included 20 patients with squamous carcinoma and 20 with adenocarcinoma of the lung and found similar asbestos body and fiber counts in these two groups as compared to 20 patients with pulmonary metastases and 20 with cardiovascular disease. Roggli (*56*) studied 30 selected cases of lung cancer with some history of asbestos exposure, but without asbestosis or pleural plaques. The series of Warnock et al. (*25*) included 7 of 9 cases with histologically confirmed asbestosis, and the series of Warnock and Isenberg (*67*) included 12 of 62 cases with asbestosis. These studies indicate that in populations with no appreciable occupational exposure to asbestos and with substantial exposure to cigarette smoke, there is little evidence for a

Table 5. Asbestos content of lung tissue in reported series of patients with lung cancer.[a]

No. of cases	Method[b]	Asbestos bodies/g dried lung	Uncoated fibers/g dried lung	Reference
100	PCLM	—	0.009 (0–0.115)	(*23*)
30	SEM	11.8[c] (0–510)	0.25[c] (0.007–1.74)	(*56*)
40	TEM[d]	0.16 (0–290)	16	(*47*)
9	TEM[d]	35.6 (0.41–840)	5.83 (3.10–73.3)	(*25*)
75	TEM[d]	3.75 (0–1000)	2.18 (0.077–97)	(*67*)

[a] Values reported are the median counts for thousands (10^3) of asbestos bodies or millions (10^6) of uncoated fibers per gram of dried lung tissue, with ranges indicated in parentheses, except for the study of Gaudichet et al. (*47*), where only the mean value for total fibers per gram dried lung could be obtained from the data presented.
[b] PCLM, phase contrast light microscopy; SEM, scanning electron microscopy; TEM, transmission electron microscopy.
[c] Values multiplied by a factor of 10 (approximate ratio of wet to dry lung weight) for purposes of comparison.
[d] In these three studies, asbestos bodies were counted by conventional light microscopy.

Table 6. Asbestos content of lung tissue in reference or control populations.[a]

No. of cases	Method[b]	Asbestos bodies/g dried lung	Uncoated fibers/g dried lung	Reference
100	PCLM	—	0.007 (0–0.521)	(*23*)
10	SEM[c]	0.020[d] (0–0.22)	0.034[d] (0.016–0.056)	(*22*)
28	SEM	—	0.25 (0–4.8)	(*45*)
20	TEM[c]	0.28[d] (0.02–0.84)	1.29[d] (0.260–7.55)	(*27*)
20	TEM[c]	0.18 (0–3.2)	11.2	(*47*)
23	TEM	—	0.62	(*72*)

[a] Values reported are the median counts for thousands (10^3) of asbestos bodies or millions (10^6) of uncoated fibers per gram of dried lung tissue, with ranges indicated in parentheses, except for the study of Gaudichet et al. (*47*), where only the mean value for total fibers per gram dried lung could be obtained from the data presented.

[b] PCLM, phase contrast light microscopy; SEM, scanning electron microscopy; TEM, transmission electron microscopy.

[c] In these three studies, asbestos bodies were counted by conventional light microscopy.

[d] Values multiplied by a factor of 10 (approximate ratio of wet to dry lung weight) for purposes of comparison.

contributing role for asbestos in these cancers (*23,47*) and that in populations with some occupational exposure to asbestos but without asbestosis, the tissue asbestos burden is greater than that of the general, nonexposed population (*25,56,67*). These studies do not prove whether asbestos is a substantial contributing factor to the lung cancers in those patients exposed to asbestos who do not have asbestosis.

These observations are not surprising when one considers that 85 to 90% of lung cancers occurring annually in the United States are attributable to cigarette smoking, whereas as few as 2% of cases may be related to asbestos exposure (*68*). However, the association of lung cancer with asbestosis is truly astounding, with somewhere between 40 and 65% of individuals with asbestosis ultimately succumbing to carcinoma of the lung (*1,28,69*). Indeed, it is quite possible that the excess numbers of lung cancers occurring in asbestos-exposed populations are entirely attributable to those occurring in individuals with asbestosis (*61*), although others have argued that it is the amount of asbestos exposure rather than the fibrotic reaction that is the determining factor (*67*). In order to resolve this issue, it will be necessary to study tissue fiber burdens in cohorts of asbestos workers who do not have asbestosis. One could then use logistic analysis to compare fiber burden levels and smoking history in individuals dying from lung cancer versus other causes of death. In this manner, it could be determined whether differences are explainable by smoking habit alone or if fiber burden is a separate contributing factor. Fiber dimensions are probably important as well, and in this regard, Lippmann (*35*) concluded in his review of the human and animal data that it is primarily fibers greater than 10 μm in length and greater than 0.15 μm in diameter that are responsible for development of lung cancer.

Further study of the possible role of nonasbestos mineral fibers and nonfibrous mineral particles in the pathogenesis of lung cancer is also needed. It has been suggested that the increased numbers of mineral fibers and particles found in the lungs of smokers with lung cancer as compared to a group of age-matched smokers without lung cancer may play a pathogenetic role (*70*). Alternatively, smokers who develop lung cancer may simply have genetically determined less efficient clearance mechanisms for fibers, particles, tars, and associated carcinogens that may find their way into the respiratory tract (*71*).

Normal Lungs

Determination of background levels of fibers to be expected in the general population is an extraordinarily difficult task because it is no simple matter to define what is normal or to exclude unknown exposures. Several investigators have established ranges of fiber burdens identified in control or reference populations (*22,23,27,45,47,72*), and some of these are summarized in Table 6. The variations in reported values can largely be accounted for by methodologic differences and patient selection criteria. In any analysis of fiber burden data in a population with a given disease, it is of critical importance to compare the findings with those of an appropriate reference or control population for which the same analytical technique was employed.

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